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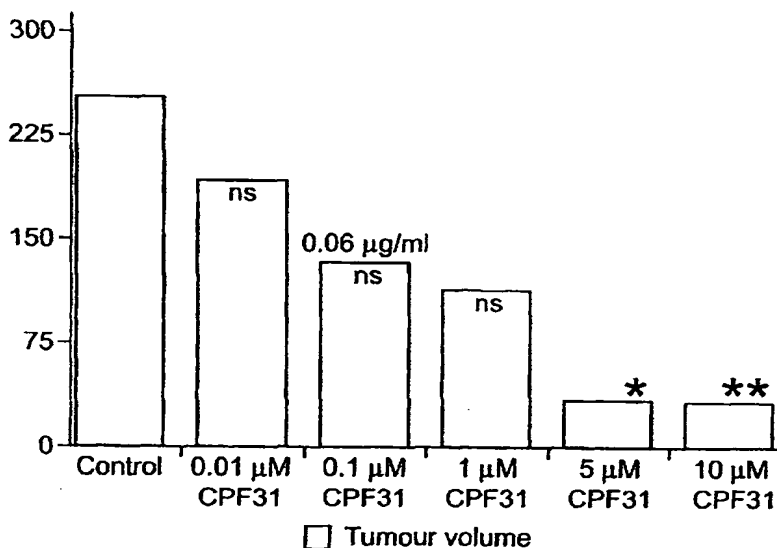
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[Continued on next page]

(54) Title: NUCLEOTIDE PHOSPHORAMIDATES AS ANTICANCER AGENTS



* p=0.096 vs control; ** p=0.094 vs control

(57) Abstract: Phosphoramidate derivatives of nucleotides and their use in the treatment of cancer are described. The base moieties of, for example, each of deoxyuridine, cytarabine, gemcitabine and citidine may be substituted at the 5-position. The phosphoramidate moiety has attached to the P atom an aryl-O moiety and an α -amino acid moiety. The α -amino acid moiety may correspond to or be derived from either a naturally occurring or a non-naturally occurring amino acid.



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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07H19/10 A61K31/7068 A61K31/7072 A61P35/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07H A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EP0-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/109697 A1 (SHEPARD H MICHAEL ET AL) 12 June 2003 (2003-06-12) the whole document	1-6,8-26
X	WO 01/07454 A (GROZIAK MICHAEL P ; SHEPARD H MICHAEL (US); CHAN MING FAI (US); NEWBIO) 1 February 2001 (2001-02-01) the whole document ----- -/--	1-6,8-26
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
Date of the actual completion of the international search 20 October 2004		Date of mailing of the international search report 20 JAN 2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer de Nooy, A

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LACKEY D B ET AL: "Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound NB1011 by thymidylate synthase" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 61, 2001, pages 179-189, XP002204184 ISSN: 0006-2952 figure 1 the whole document</p> <p>-----</p>	1-6,8-26
X	<p>S.A. HARRIS ET AL.: "Synthesis and antiviral evaluation of phosphoramidate derivatives of (E)-5-(2-bromovinyl)-2'-deoxyuridine" ANTIVIRAL CHEMISTRY AND CHEMOTHERAPY, vol. 12, 2001, pages 293-300, XP008037325 figure 1</p> <p>-----</p>	1-6, 8-21,26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/003148

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see extra sheet

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6 (in part), 8-26 (in part)

Chemical compounds of formula I of claim 1 where Ar is unsubstituted phenyl, uses, methods, compositions and processes pertaining thereto.

2. claims: 1-6 (in part), 8-26 (in part)

Chemical compounds of formula I of claim 1 where Ar is a substituted phenyl as in claim 6, uses, methods, compositions and processes pertaining thereto.

3. claims: 1-6 (in part), 8-26 (in part)

Chemical compounds of formula I of claim 1 where Ar is not as defined in claim 6, uses, methods, compositions and processes pertaining thereto.

4. claims: 7 (in full), 8-19 (in part)

Chemical compounds of formula II of claim 7.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/003148

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003109697 A1	12-06-2003	US 2001034440 A1	25-10-2001
		US 6339151 B1	15-01-2002
		AT 212661 T	15-02-2002
		AU 753155 B2	10-10-2002
		AU 2464699 A	09-08-1999
		BR 9907736 A	17-10-2000
		CA 2317505 A1	29-07-1999
		CN 1291228 T	11-04-2001
		DE 69900841 D1	14-03-2002
		DE 69900841 T2	02-10-2002
		DK 1045897 T3	13-05-2002
		EP 1167972 A2	02-01-2002
		EP 1045897 A1	25-10-2000
		ES 2172303 T3	16-09-2002
		HK 1030624 A1	14-06-2002
		JP 3265304 B2	11-03-2002
		JP 2001220397 A	14-08-2001
		JP 2002500880 T	15-01-2002
		PT 1045897 T	31-07-2002
		WO 9937753 A1	29-07-1999
		US 6245750 B1	12-06-2001
<hr/>			
WO 0107454 A	01-02-2001	AU 775601 B2	05-08-2004
		AU 6231900 A	13-02-2001
		BR 0012677 A	01-07-2003
		CA 2379988 A1	01-02-2001
		CN 1390227 T	08-01-2003
		EP 1200455 A1	02-05-2002
		JP 2003505466 T	12-02-2003
		MX PA02000763 A	12-08-2002
		WO 0107454 A1	01-02-2001
		US 6683061 B1	27-01-2004
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